

HPV Vaccination to prevent HPV-associated cancers

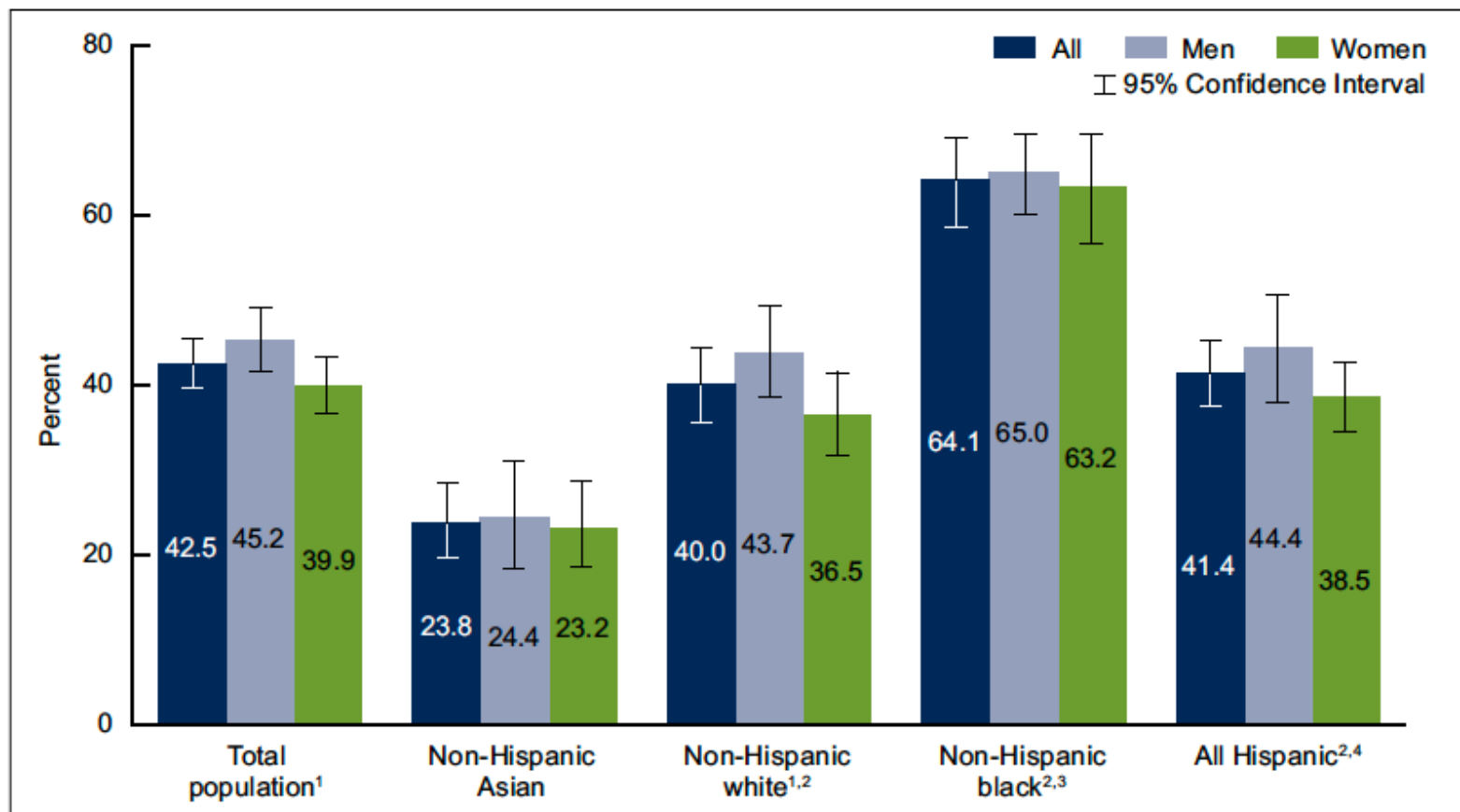
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Center for Cancer Research, NCI

Demystifying Medicine
Bethesda, Maryland
January 23, 2018

Disclosures

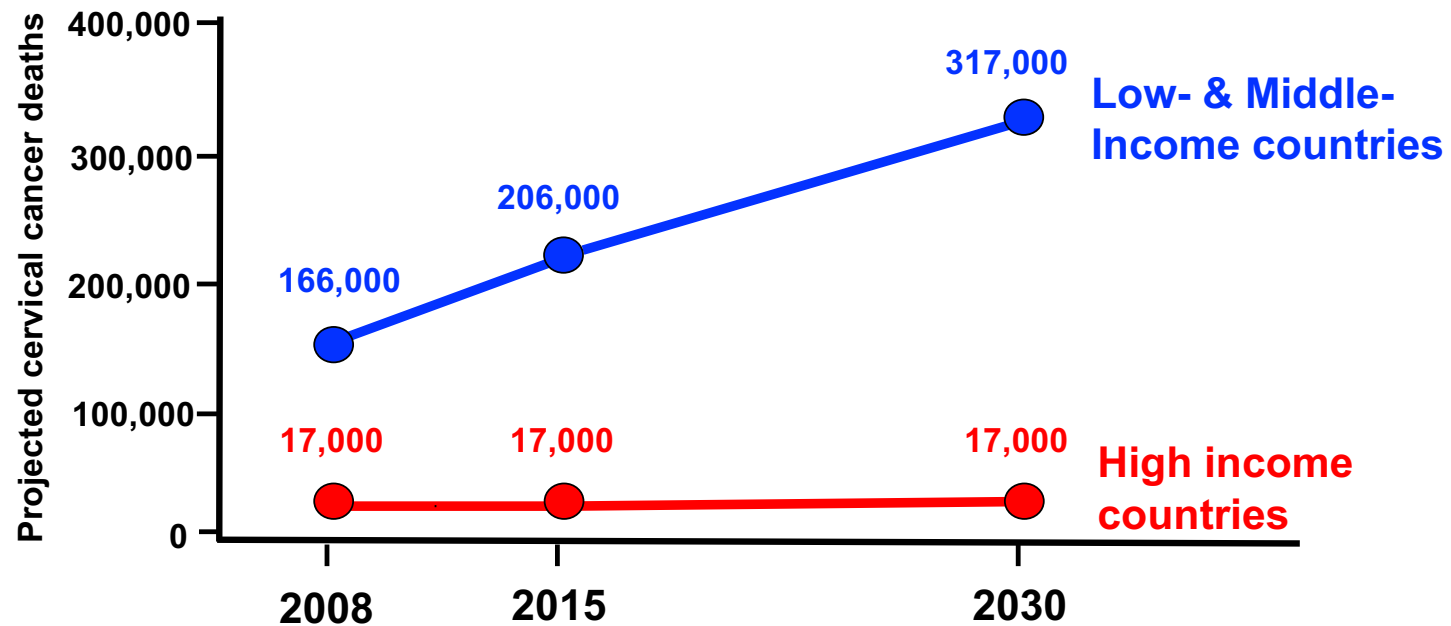
- National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. I am an inventor.
- NIH has licensed L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine.
- ***I will discuss potential off-label uses of the EMA/FDA-approved vaccines: protecting against HPV-positive oropharynx cancer and fewer vaccine doses***
- Licensees of other NIH technologies of which I am an inventor: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax

More than 40% of men & women 18-59 have genital HPV infection



McQuillan et al, NCHS Databrief 280, 2017

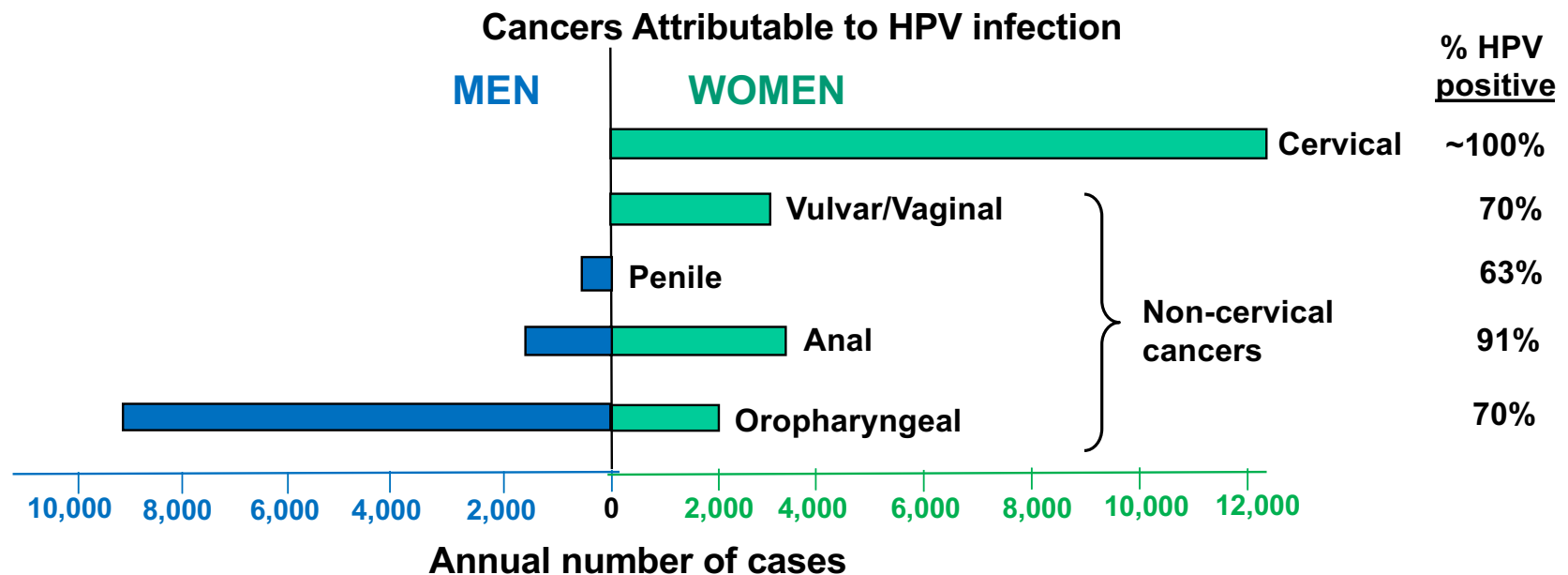
IARC's Globocan 2012 projection: Cervical cancer mortality rates continue to increase in Low- & Middle-income countries (LMIC's)



- In LMIC's, cervical cancer represents ~90% of HPV-associated cancer

Projections developed from Globocan 2012

USA: HPV-associated cancers affect both sexes



- Total number of HPV-positive cancers = ~31,000. 65% women; 35% men
- HPV16/18: Accounts for 70% of cervical cancers, 90% of non-cervical cancers
- Pap screening has reduced cervical cancer incidence by ~80%
- Incidence of HPV-positive oropharynx cancer 1988-2004 increased >3-fold

Adapted from Viens, et al., MMWR, 2016

***First Generation
HPV Vaccines***

***Many Collaborators: If you want to go quickly, go alone;
If you want to go far, go together***

Laboratory of Cellular Oncology, CCR, NCI

John Schiller

Patricia Day

Rhonda Kines

Cynthia Thompson

Tara Berman

Nicolas Cuburu

Susana Pang

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Chris Buck, Diana Pastrana - *LCO, CCR, NCI Bethesda*

Aimee Kreimer, Allan Hildesheim, Mark Schiffman, Mahboobeh Safaeian, Ligia Pinto - *DCEG, NCI, Bethesda*

Peter Choyke, Marcelino Bernardo - *Molecular Imaging, CCR, NCI, Bethesda*

Jeffrey Roberts – *FDA, Rockville*

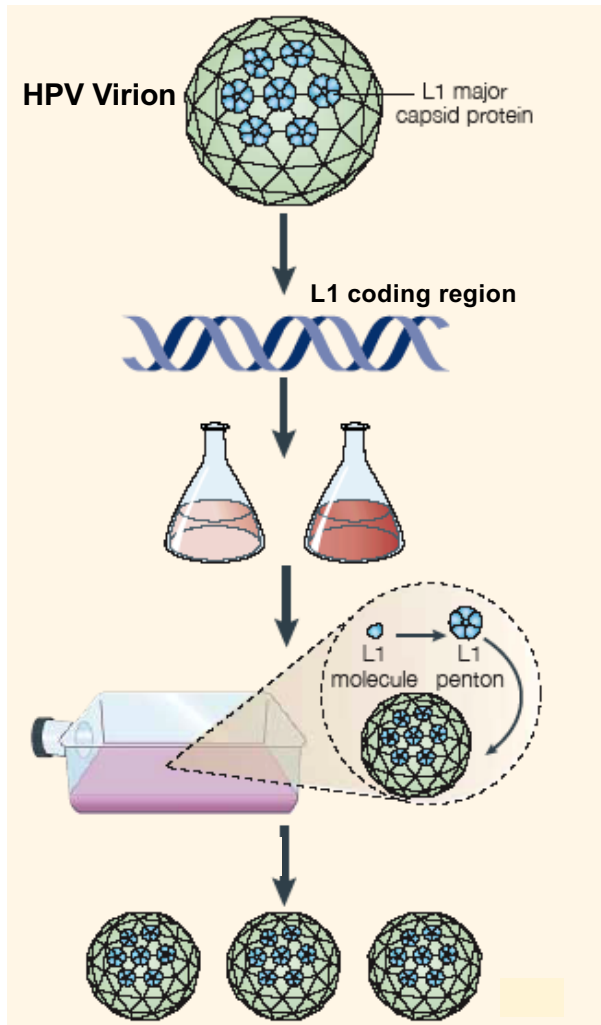
Rolando Herrero – *IARC, Lyon, France*

Bryce Chackerian - *University of New Mexico*

Reinhard Kirnbauer - *University of Vienna, Austria*

Choosing an appropriate molecular target for a preventive HPV vaccine

- **Licensed vaccines: mainly preventive, induce neutralizing antibodies**
- **HPVs contain viral oncogenes (E5, E6, E7); need subunit vaccine lacking oncogenes.**
- **Two HPV proteins can induce neutralizing antibodies: capsid proteins L1 and L2.**
 - ***L1 contains the most immunogenic neutralization epitopes; conformational***
- ***OUR HYPOTHESIS: L1 self-assembles, makes empty particles with correct conformation, induce high levels of neutralizing antibodies.***



Prophylactic HPV Vaccines Are L1 Virus-Like Particles (VLPs)

Insert L1 in Baculovirus expression vector

Produce L1 in insect cells

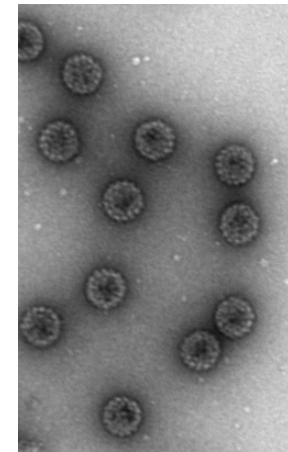
L1 spontaneously assembles into VLPs

L1 VLP vaccination Induces high titers of neutralizing antibodies

Shown first for BPV-1, then for HPV16

Non-infectious, Non-oncogenic

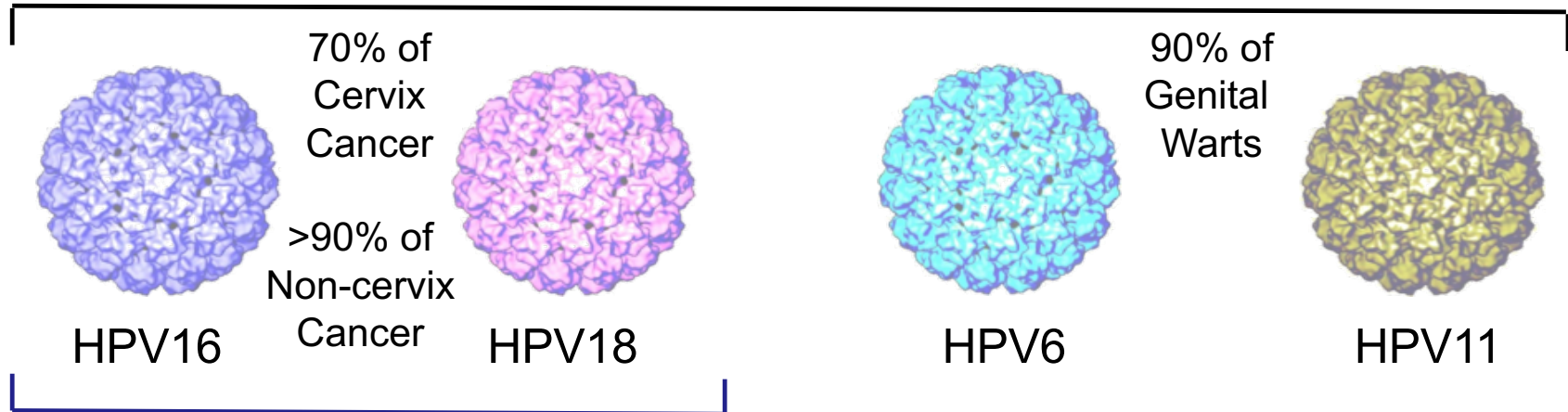
HPV16 L1 VLPs



Reinhard Kirnbauer et al. PNAS 1992; J Virol 1993

First generation HPV vaccines: Composed of Multiple Types of HPV L1 VLPs

Gardasil (quadrivalent, Merck)



Cervarix (bivalent, GlaxoSmithKline)

Three intramuscular injections over 6 months



Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink^a

Julianne Gee^{a,*}, Allison Naleway^b, Irene Shui^c, James Baggs^a, Ruihua Yin^c, Rong Li^c, Martin Kulldorff^c, Edwin Lewis^d, Bruce Fireman^d, Matthew F. Daley^e, Nicola P. Klein^d, Eric S. Weintraub^a

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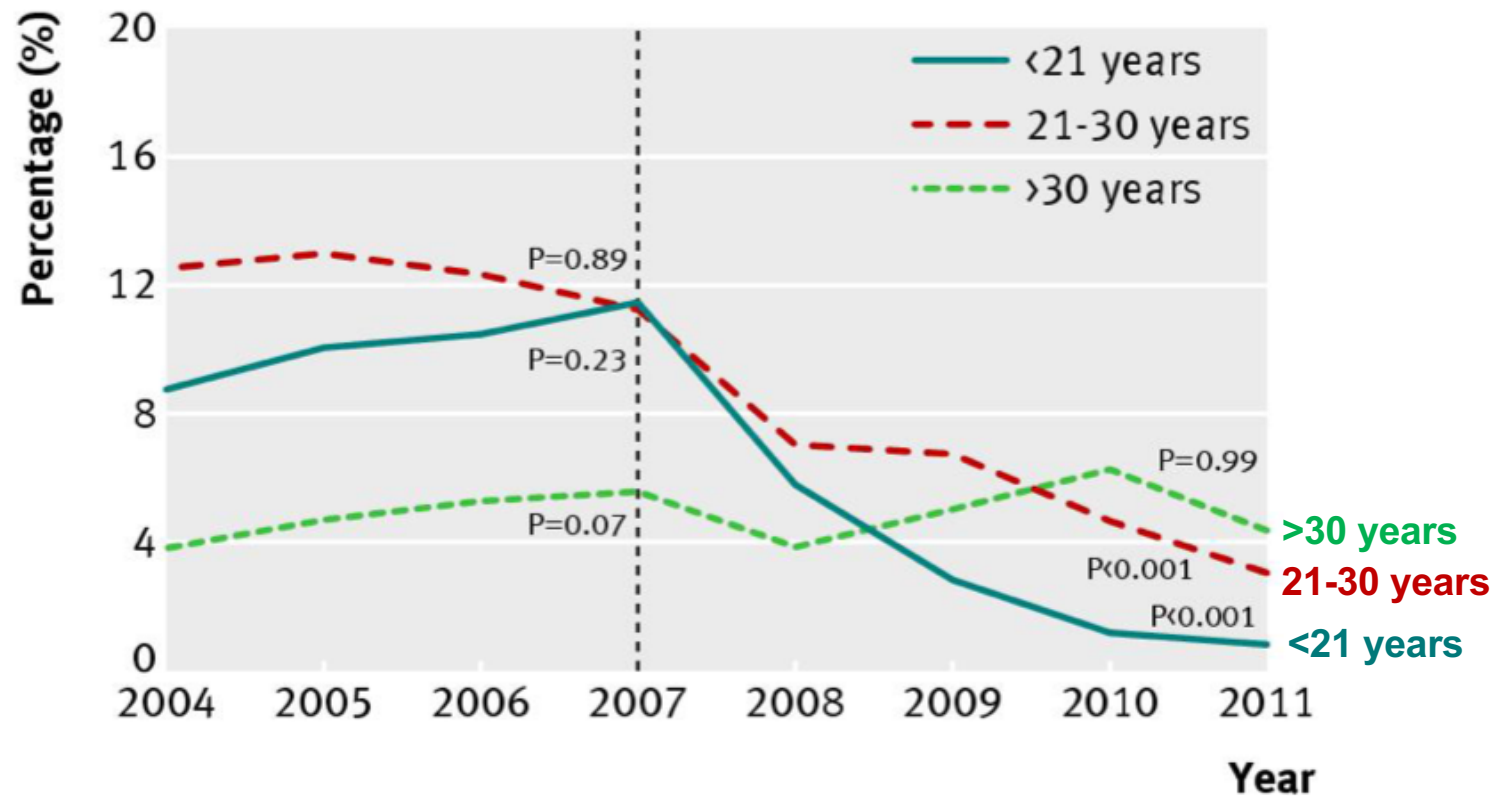
- Prospective post-licensure assessment of 600,558 doses (Gardasil) from 7 managed care organizations
- ***No excessive vaccine-related increased risk to prespecified outcomes:*** Guillan-Barré syndrome, stroke, venous thromboembolism, appendicitis, seizure, *allergic reactions*
 - Prespecified outcomes derived from CDC analysis from VAERS (Vaccine Adverse Events Reporting System): Slade et al, JAMA 2009
 - ***Rate of anaphylaxis (1 case, 26 y.o.) similar to other vaccines***
 - Rate of fainting similar to that of other adolescent vaccines
- Similar conclusions in recent review: Gee et al, Hum Vaccin Immunother 2016

Short-term Population-wide Impact of HPV Vaccination

Goals of HPV Vaccination

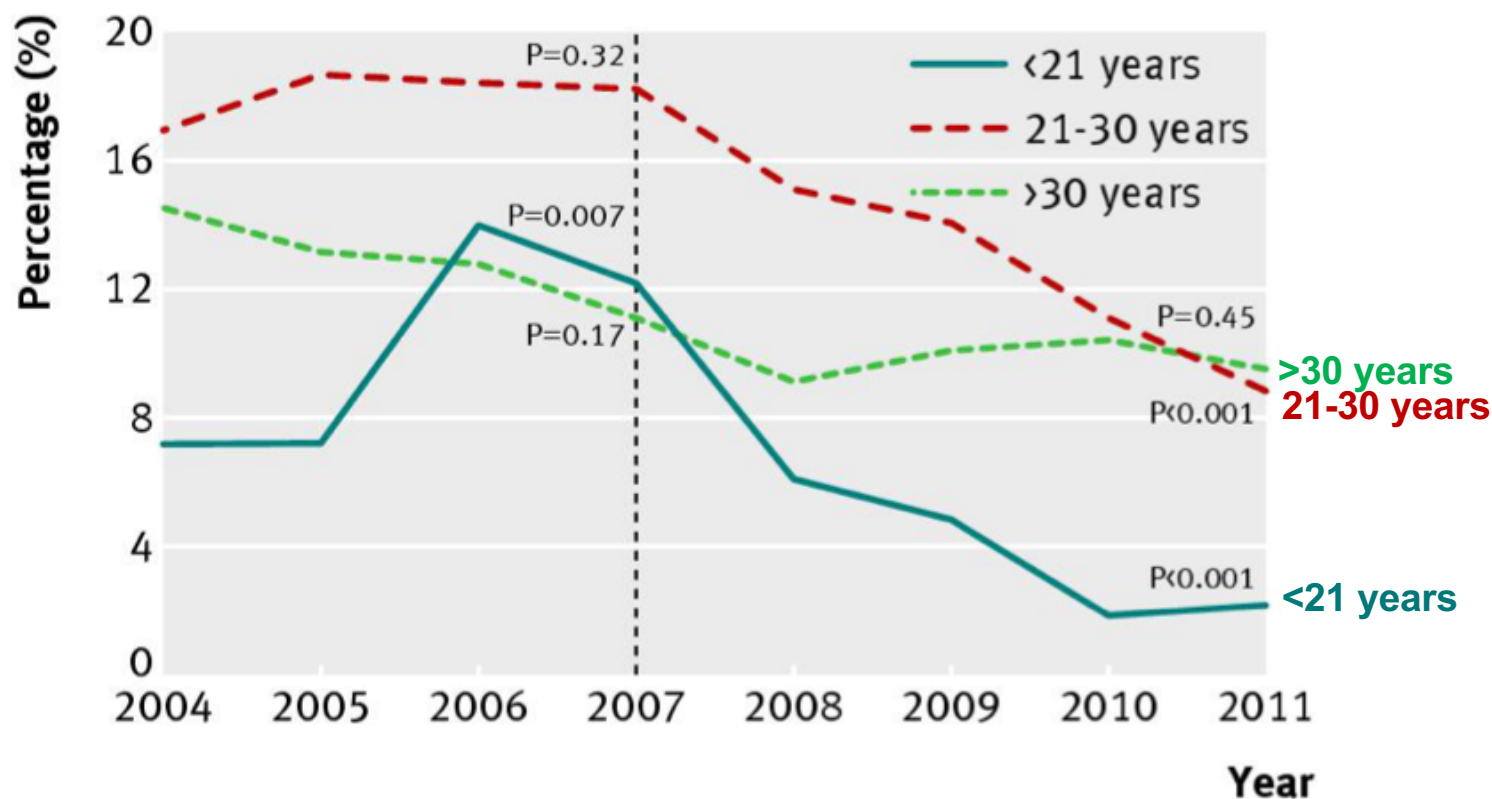
- **Directly reduce risk of infection and disease in vaccinees**
- **Indirectly reduce risk by reducing prevalence of “HPV vaccine types” in general population (herd immunity)**

Age-dependent decrease in genital warts in Australian women after HPV Vaccine Implementation in 2007



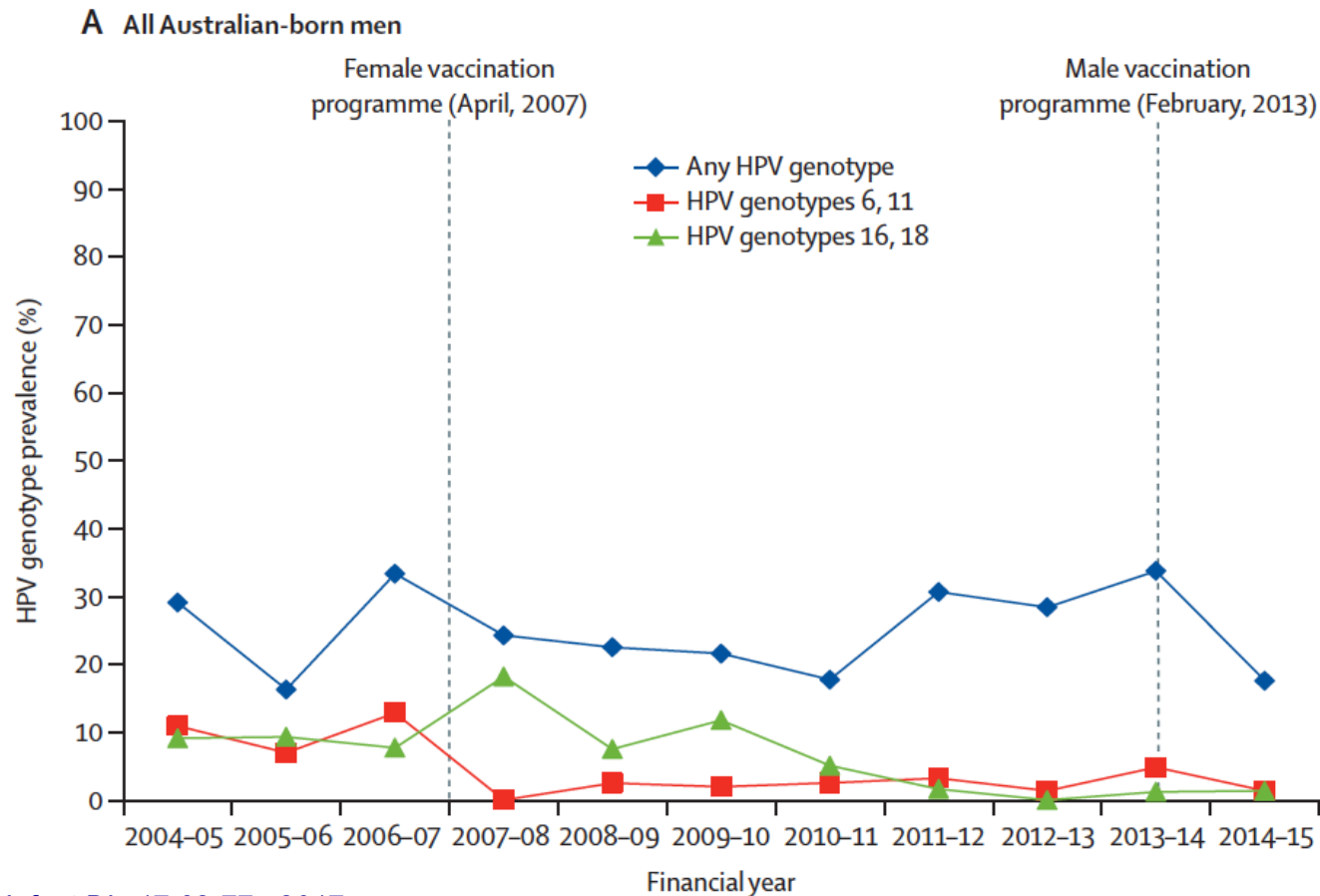
Ali et al, BMJ 2013

Herd Immunity: Decreased incidence of genital warts in heterosexual Australian men following female HPV vaccine implementation in 2007



Ali et al, BMJ 2013

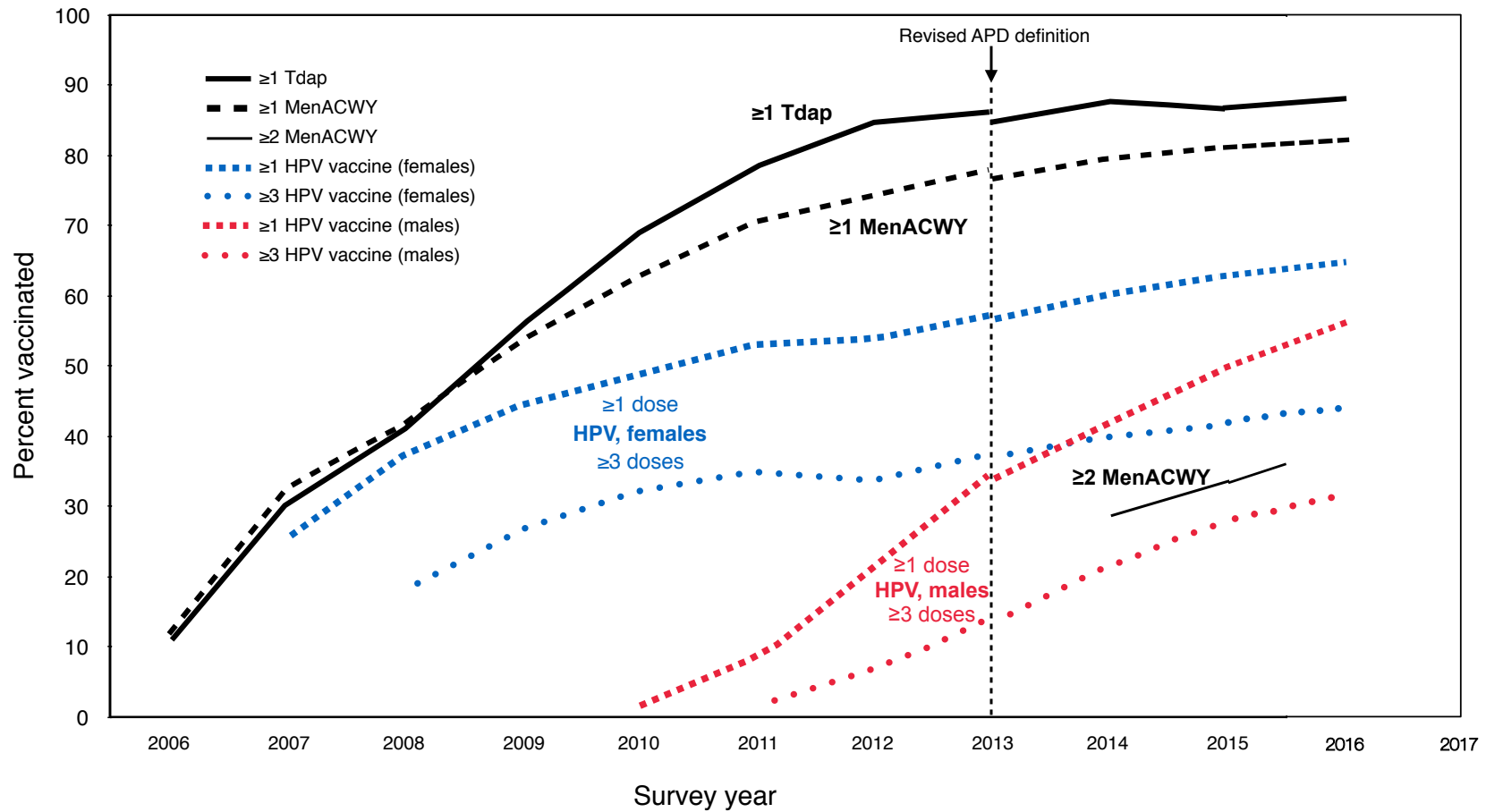
Herd immunity: Decreased prevalence of HPV6/11/16/18 in heterosexual Australian men following female HPV vaccine implementation in 2007



Chow et al, Lancet Infect Dis 17:68-77, 2017

Trends in U.S. Vaccination Rates: Ages 13-17 Years

MMWR Vol. 66, #33, August 25, 2017



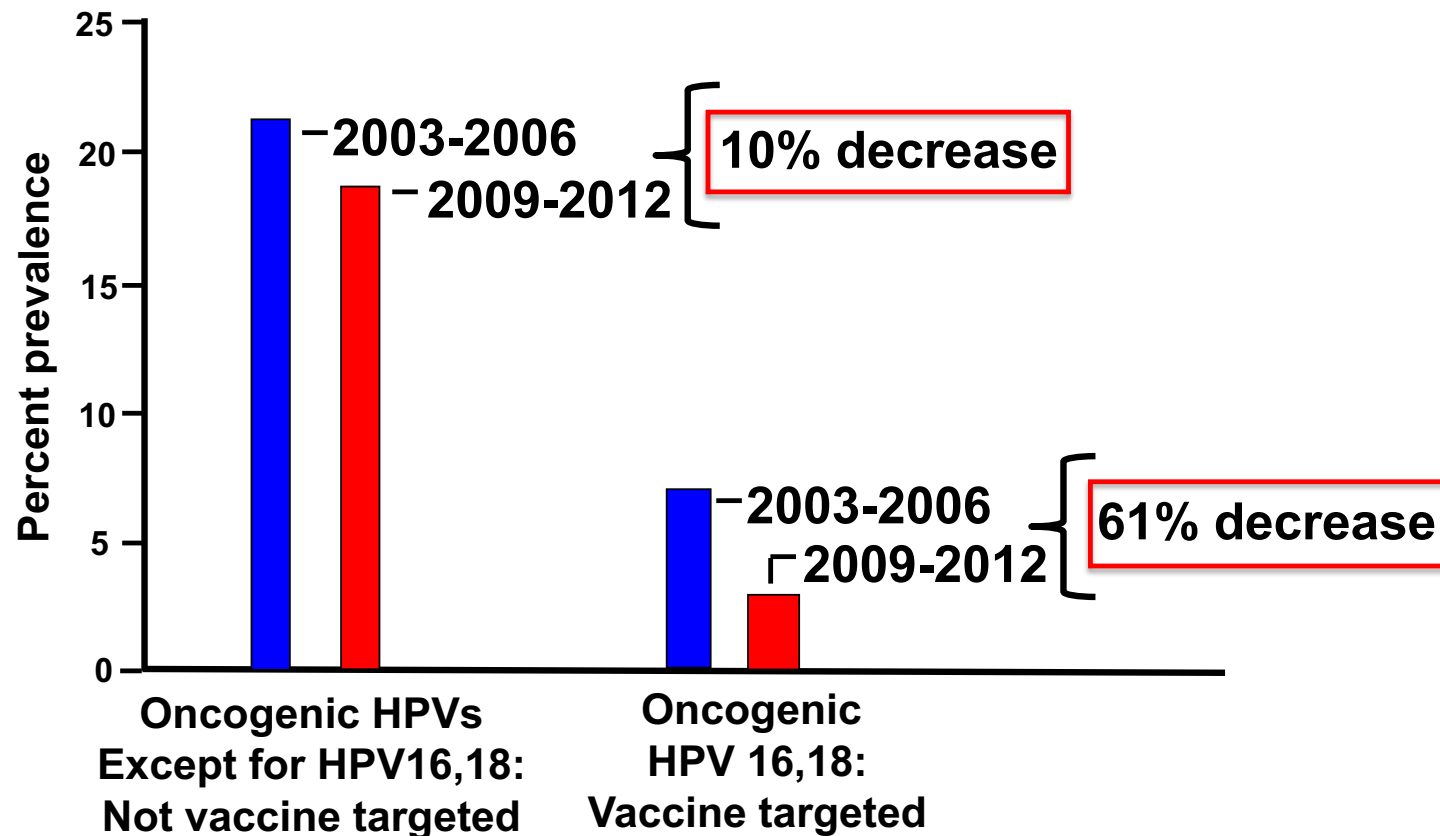
Parents' Top 5 Reasons for not vaccinating their Children with the HPV Vaccine (CDC, 2013)

Parents of girls		
Reason	%	(95% CI)
Lack of knowledge	15.5	(13.0–18.5)
Not needed or necessary	14.7	(12.5–17.3)
Safety concern/Side effects	14.2	(11.8–16.8)
Not recommended	13.0	(10.8–15.5)
Not sexually active	11.3	(9.1–13.9)

Parents of boys		
Reason	%	(95% CI)
Not recommended	22.8	(20.6–25.0)
Not needed or necessary	17.9	(15.9–20.1)
Lack of knowledge	15.5	(13.7–17.6)
Not sexually active	7.7	(6.4–9.2)
Safety concern/Side effects	6.9	(5.6–8.5)

Stokley et al, MMWR 63:620-4, July 25, 2014

Decreased prevalence of HPV16/18 in the US despite limited HPV vaccine uptake: 14-19 year old girls (51% received 1 or more doses)

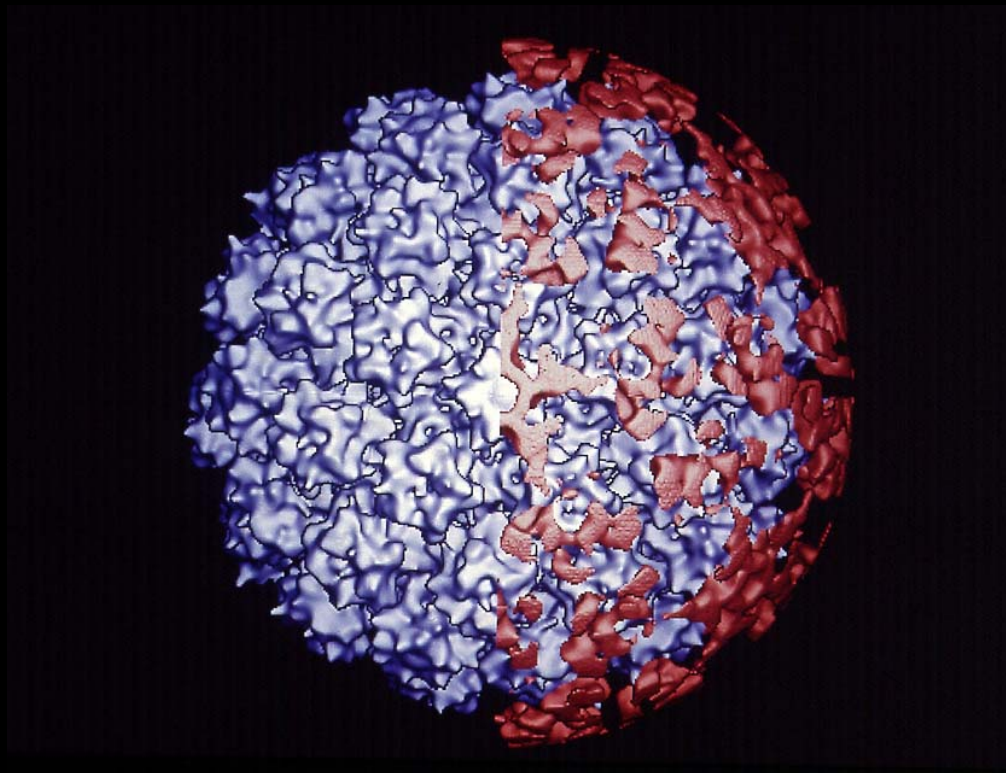


Adapted from Markowitz et al, Pediatrics 2016

High Efficacy of VLP Vaccine

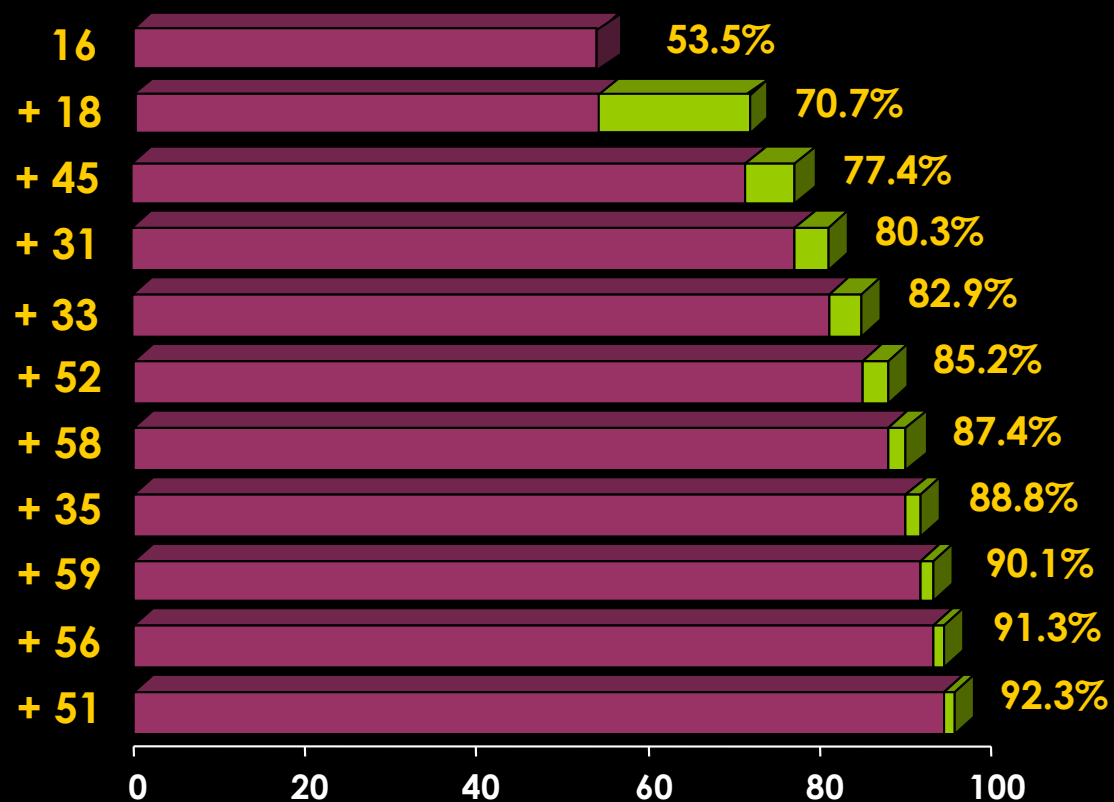
- **Repetitive structure of VLP intrinsically immunogenic**
- **Tissue-associated neutralizing antibodies exudated at potential sites of infection**
 - **Levels of exudated antibodies high, similar to serum levels, not lower levels of non-disrupted genital tract**
- **HPV highly susceptible to neutralizing antibodies**
- **For further discussion: see Schiller & Lowy, Vaccine 2018**

*Neutralizing L1 Antibodies (in red) Bound to
Papillomavirus Particle*



***Second generation
vaccine: Protecting
against more HPV
types***

Further reduction in cervical cancer by adding more HPV Types to L1 VLP Vaccine



Adapted from Munoz et al, *Int J Cancer* 111: 278-85, 2004

***Increasing HPV vaccine
uptake: Safely reducing
the number of doses***

Moving to two vaccine doses for young adolescents

- Immune response in girls and boys <15 years old stronger than older teenagers
- Young adolescents: 2 doses separated by 6 months produce an immune response even greater than the efficacy trials
 - Immunogenicity of 9-valent vaccine: Iverson et al., JAMA. 316: 2411-21, 2016
- ***October 2016: FDA approves and ACIP recommends 2 doses for 9-valent vaccine for adolescent girls and boys 9-14***

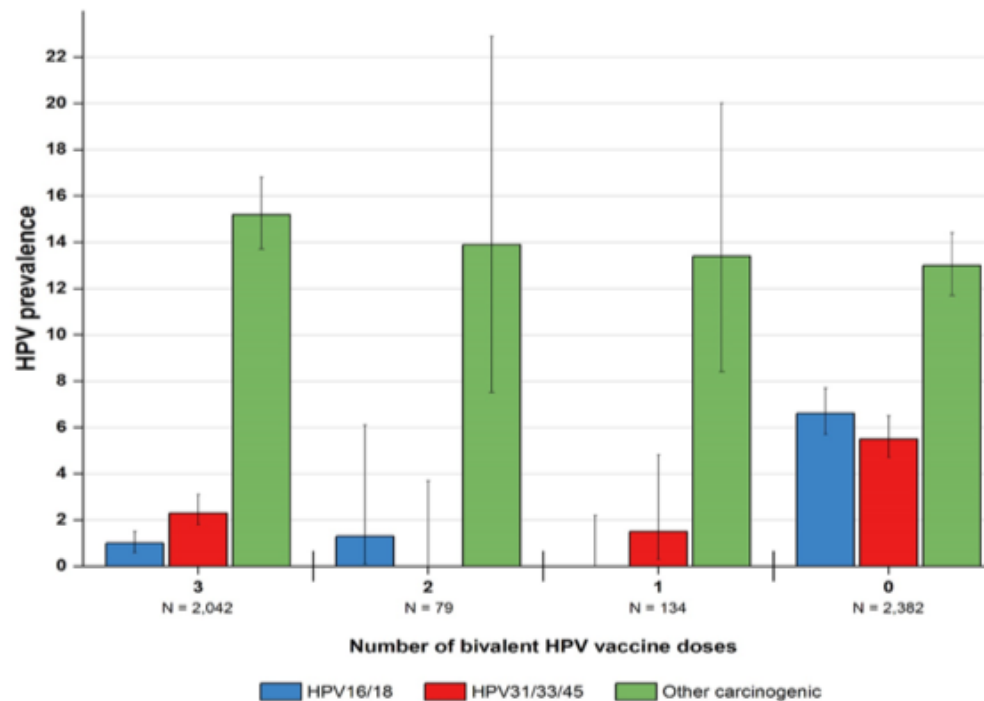
***Might a single HPV
vaccine dose confer
years of protection?***

A challenge: Projected limited impact on worldwide cervical cancer from current global HPV vaccination rates

- Only ~3% of eligible women in Low- and Middle-income countries (LMICs) have been vaccinated
 - ~33% of eligible women in industrialized world have been vaccinated
- Women in LMICs account for ~90% of worldwide cervical cancer mortality; ~8% of worldwide female cancer mortality
- **Widespread global uptake of HPV vaccine may require decreased costs & simplified logistics**
- **Possible solutions: Producing biosimilar vaccines and protecting vaccinees with a single dose**

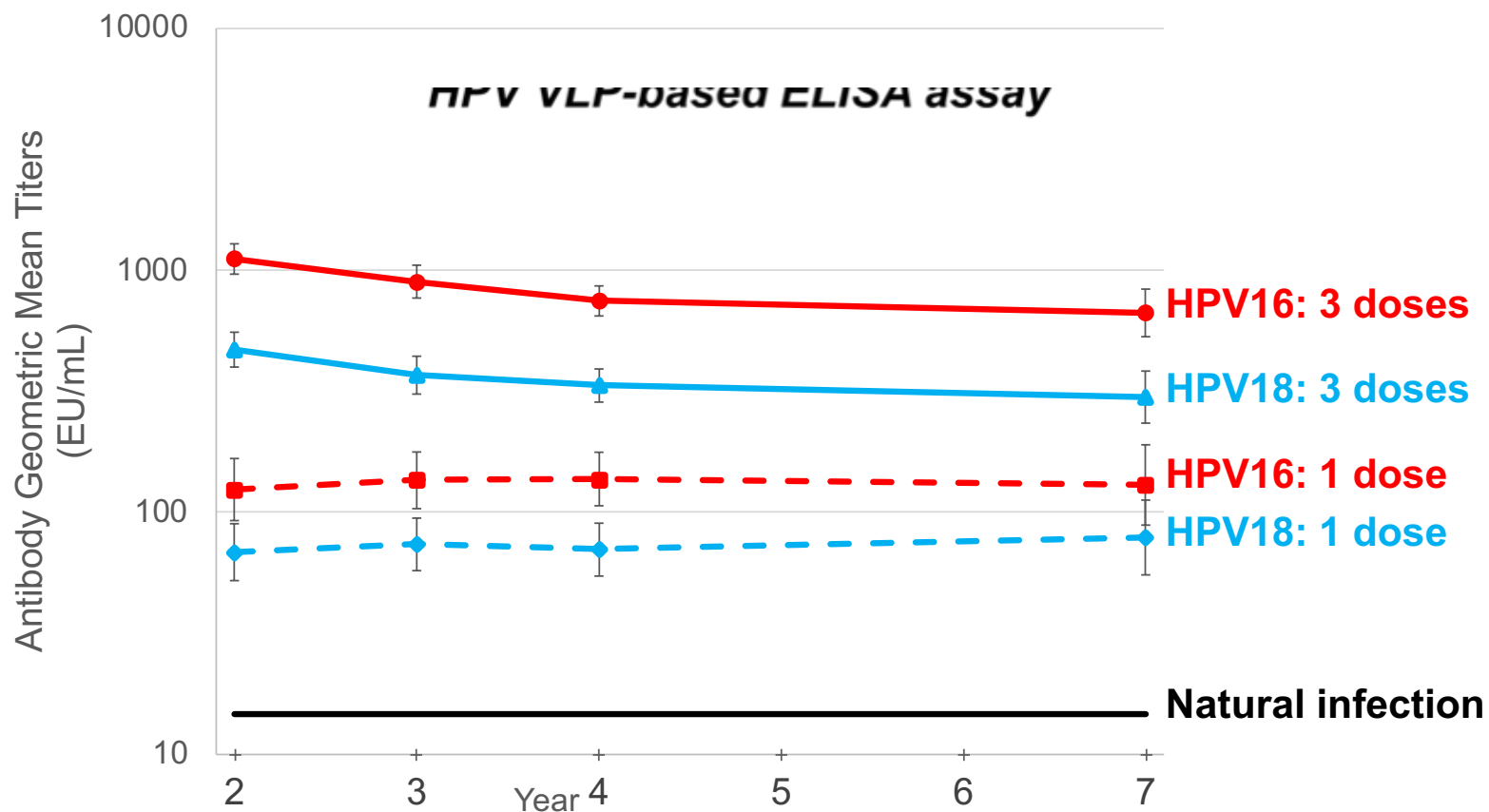
1, 2, or 3 doses of bivalent vaccine confer at least 7 years of protection against incident HPV 16/18 infection: Post-hoc analysis

Safaeian et al, J Natl Cancer Inst, published August 28, 2017



- ***Similar shorter term results in GSK PATRICIA trial: Kreimer et al, Lancet Oncol 2015***
- ***Similar shorter term Gardasil results in IARC India trial, Sandaranarayanan et al, Lancet Oncol 2016***

Stable HPV16/18 serum antibodies after bivalent HPV vaccination: Costa Rica Vaccine Trial



Safaeian M et al, JNCI, published August 28, 2017

Randomized controlled efficacy trial in Costa Rica to test efficacy of 1 dose vs. 2 doses (NCI & Gates Foundation)

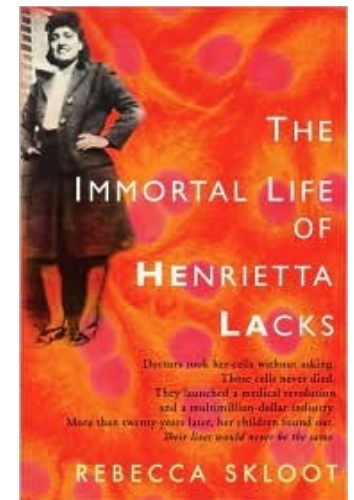
- **A 4-arm non-inferiority trial in 12-16 year old girls:** compare protection from 1 dose and 2 doses of bivalent vaccine (Cervarix, GSK) and 9-valent vaccine (Gardasil9, Merck)
 - Unethical to have a placebo arm; measure current HPV prevalence in young women in same area
- **Main hypothesis:** Protection induced by 1 dose is not inferior to 2 doses
- **Second hypothesis:** Protection will be similar for 1 dose of either vaccine (evaluates possible role of adjuvant; Merck uses alum, GSK uses AS04)
- **For more information:**
 - For 1 dose trial concept, see Kreimer et al, J Natl Cancer Inst, 2015; Kreimer et al, Vaccine, in press
 - See clinicaltrials.gov: Identifier NCT03180034

Potential impact of demonstrating 1 dose can confer strong protection

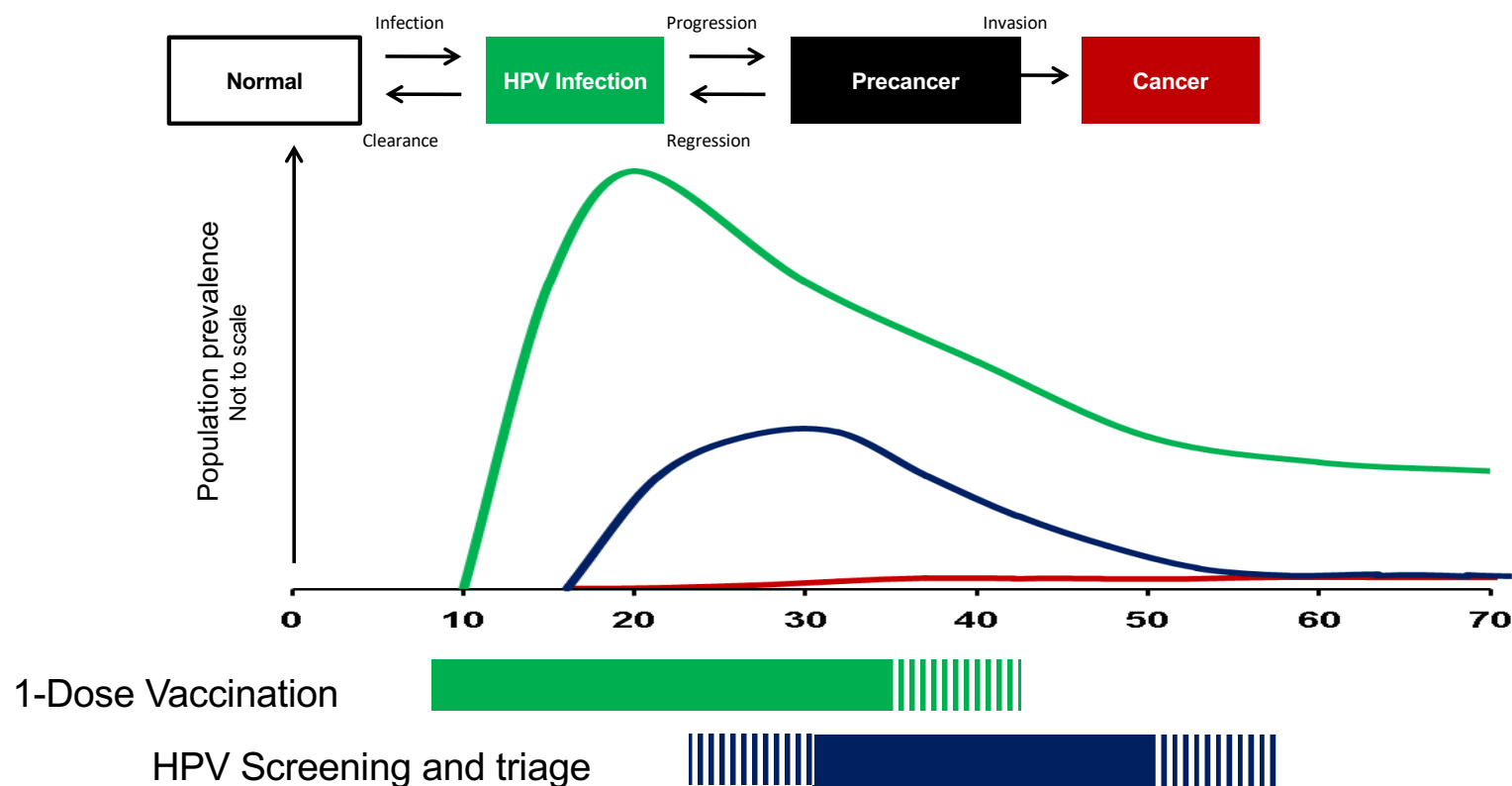
- Could establish a new minimum serum antibody titer needed for high level protection
- Could provide a strong rationale for considering a repetitive structure for future vaccines against other agents
- Could change standard of care in US & globally
 - Could save US > \$300 million each year in vaccine costs
- Could make it feasible to control the worldwide public health problem of cervical cancer and other HPV-associated cancers

Henrietta Lacks (HeLa cells) had Cervical Adenocarcinoma

- Pap smear screening: more sensitive for squamous cell carcinoma than adenocarcinoma
- ~ 90% of cervical adenocarcinoma caused by HPV16 or HPV18
- Henrietta Lacks: HPV 18 cervical adenocarcinoma not detected by cytology
- Her cancer should now be preventable by HPV vaccination or by HPV-based screening



***A longer-term goal: “Rapid” reduction in worldwide cervical cancer by
Vaccinating multiple birth cohorts of younger women & screening older women***



Bosch et al, HPV Faster, Nature Rev Clin Oncol, 2016; modified by Mark Schiffman

Summary and Conclusions

- Basic research led to identification of HPV as the cause of several cancers and to development of the HPV vaccine
- The HPV vaccine is highly effective in preventing new infection and disease caused by the HPV types targeted by the vaccine
 - The HPV vaccine can induce strong herd immunity
 - It may be possible to induce long-term protection with even a single dose
- Control of HPV-associated cancer as a worldwide public health problem may soon be feasible